

1,2,3-TRIAZOLE APPENDED L-ASCORBIC ACID WITH ANTIOXIDANT PROPERTIES

Ines Cazin¹, Ivana Kovačić¹, Andrijana Mešić¹, Višnja Stepanić², Silvana Raić-Malić¹

¹Department of Organic Chemistry, Faculty of Chemical Engineering and Tehnology, University of Zagreb, Marulićev trg 20, HR-10000 Zagreb, Croatia

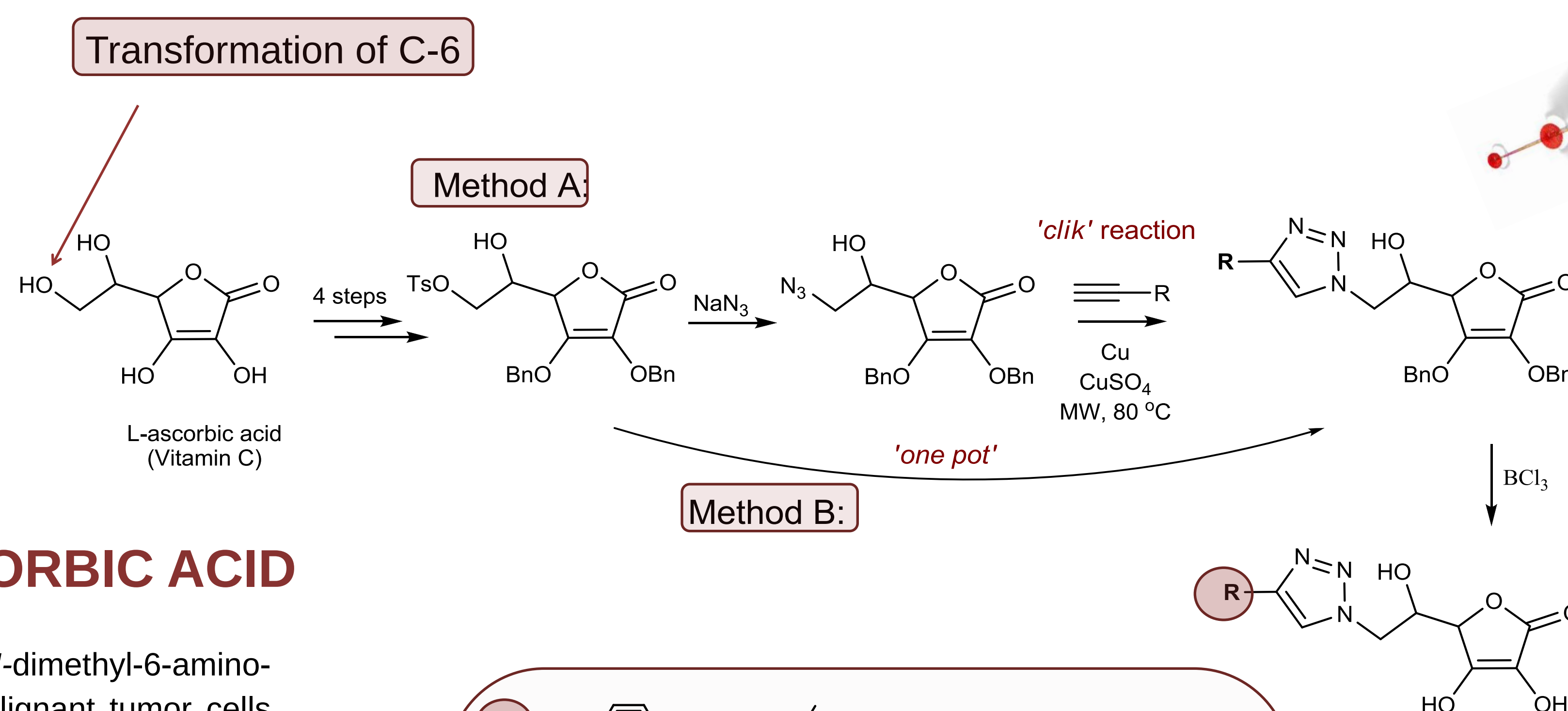
² Division of Molecular Medicine, Ruđer Bošković Institute, Bijenička cesta 54, HR-10000 Zagreb, Croatia

INTRODUCTION

1,2,3-Triazoles have attracted considerable attention in recent years because of their wide range of biological activities against various viruses, malignant cells, microorganisms and their inhibitory activities against several enzymes [1]. Various pyrimidines and purines containing L-ascorbic acid have exhibited significant antiproliferative effects against malignant human tumour cell lines [2]. Furthermore, L-ascorbic acid (vitamin C) is an electron donor, and this property accounts for all its known functions [3]. In order to link together two potentially biologically active structural motifs, new biologically interesting compounds were prepared as nucleoside mimetics in which the 1,2,3-triazole motif acts as a nucleobase surrogate while L-ascorbic acid mimics the sugar of a nucleoside. Antitumor and antiviral activity of the aforementioned compounds as well as the influence of the substituent R at the C-4 of the triazole ring on the radical scavenging capacity will be examined.

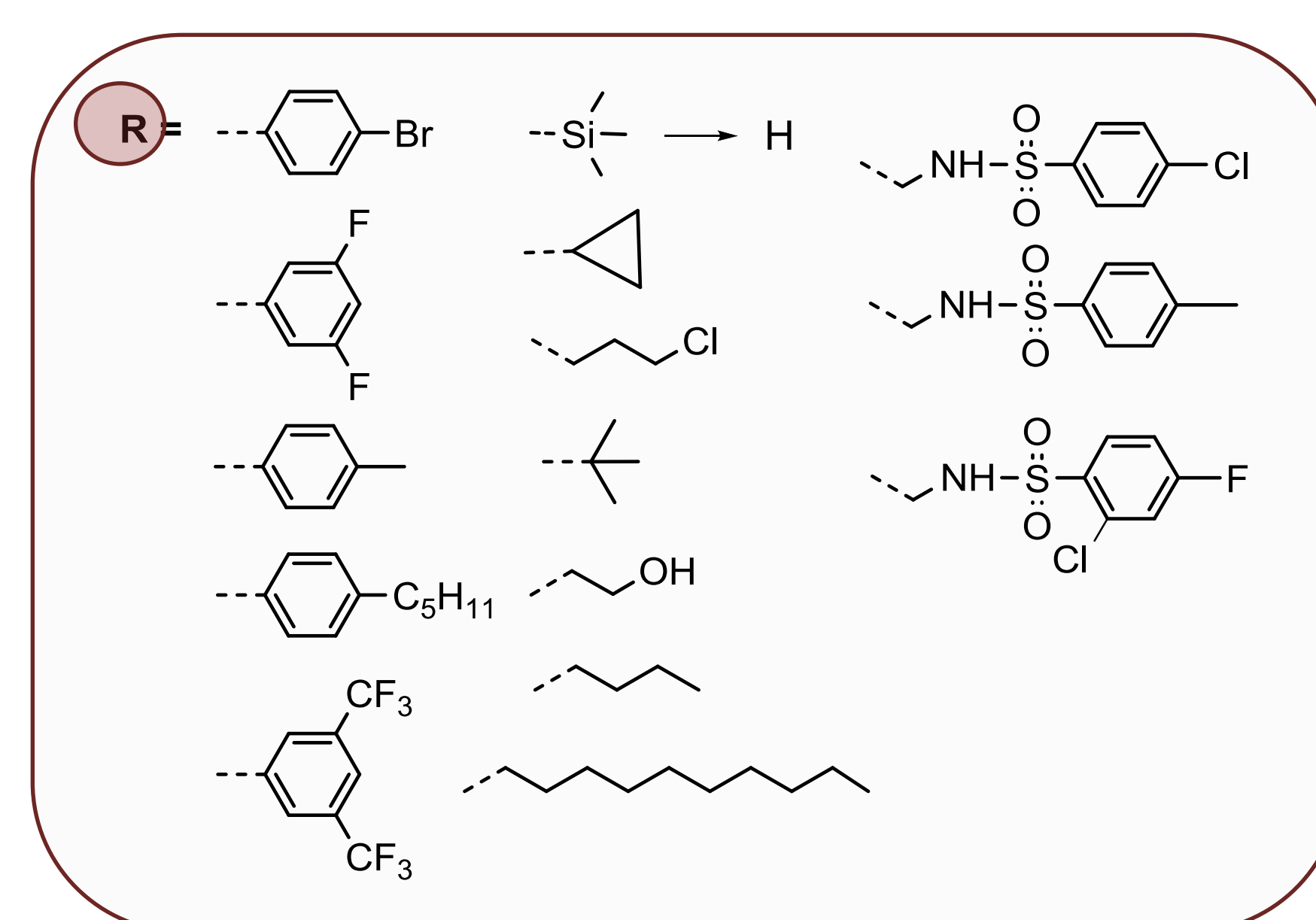
CHEMISTRY

1,4-Substituted 1,2,3-triazole derivatives of L-ascorbic acid were synthesized via 1,3-dipolar cycloaddition reaction between various acetylenes and the C-6 azide derivative of L-ascorbic acid, the so-called 'click' reaction.



BIOLOGICAL PROPERTIES OF L-ASCORBIC ACID

- Derivatives of L-ascorbic acid, e.g., 6-bromo-, 6-amino-, and *N,N*-dimethyl-6-amino-6-deoxy-L-ascorbic acid, inhibit the growth of certain human malignant tumor cell lines.
- It acts as an antioxidant and radical scavenger; protects cellular compounds against oxidative damage by free radicals and oxidants.
- L-Ascorbic acid derivatives induce apoptosis in tumor cells, possess immunostimulant activity, and/or protect against the lipid peroxidation of the biomembrane.
- It is important in the prevention of various chronic diseases.
- Vitamin C is a biologically significant reducing agent due to its 1-oxo-2-ene-2,3-diol structural moiety.



RADICAL SCAVENGING CAPACITY

- *In silico* predictions of the radical scavenging (RS) capacity of L-ascorbic acid and its 4-substituted 1,2,3-triazol-1-yl derivatives were made by density functional theory (DFT) calculations.
- Effects of the substituents R on RS capacity and acidity of the new molecules were observed.

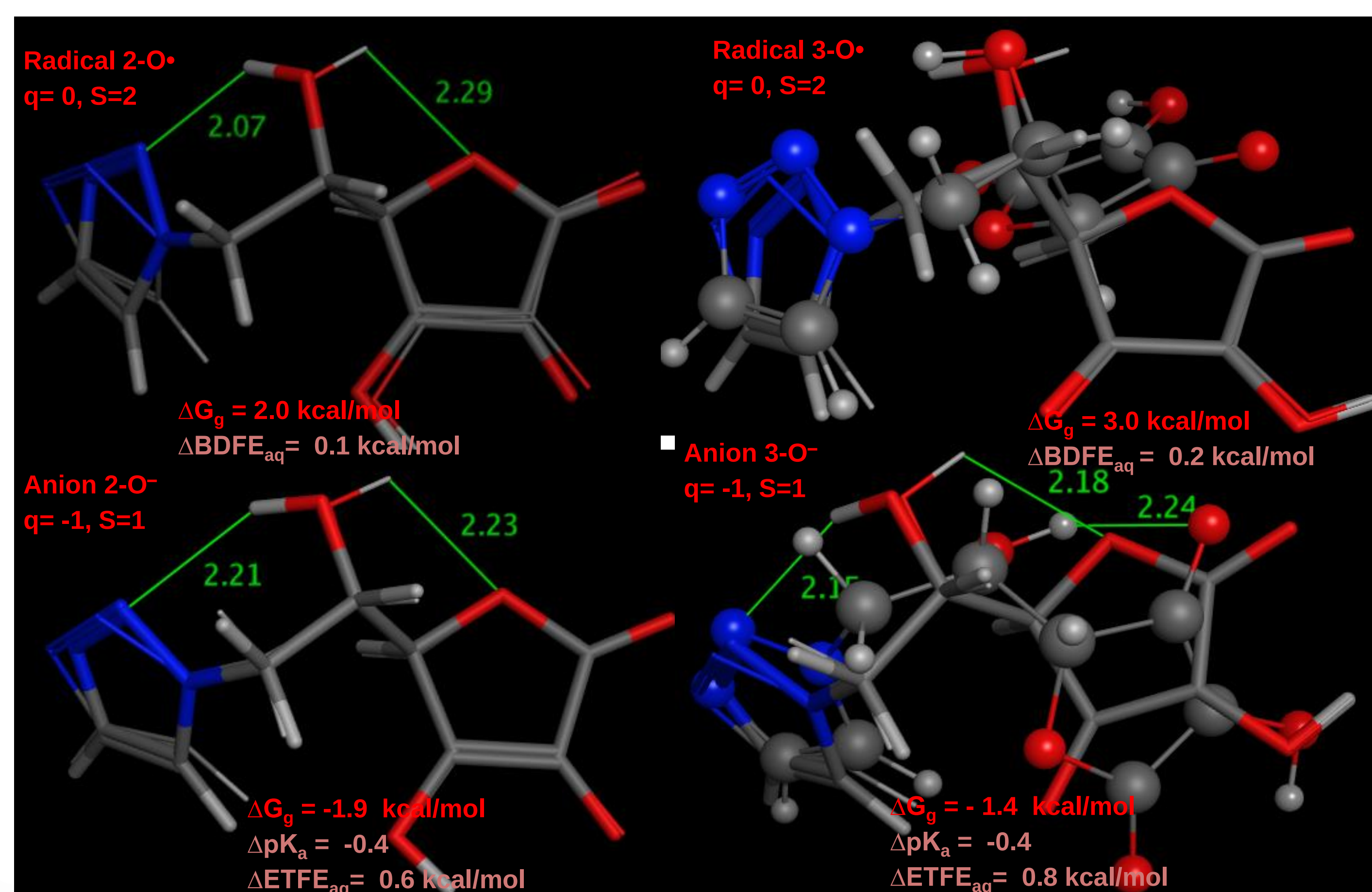


Figure 1. Geometries of neutral monoradicals and monoanions for the simplest conjugate **R = H**.

Comparison of conformations with H-bond between C-5 OH and furan oxygen or triazole (stick). Structures with ball-atoms are those with H-bond between C-5 OH and furan 3-O group.

CONCLUSION

- The prepared compounds present an interesting class of compounds with potential antitumor and antiviral activities.
- On the basis of calculations, it can be expected that conjugates of vitamin C and triazole are somewhat more acidic than vitamin C alone.
- BD(F)E, representing net free energy of the studied mechanisms, may be used as the most reliable parameter for comparison of radical scavenging capacity of conjugates with the parent fragment – vitamin C.
- Experimental measurement of RS capacity and their comparison with the calculated values is foreseen.

LITERATURE

- [1] S. Raić-Malić, A. Mešić, Curr. Med. Chem. 22 (2015) 1462-1499.
- [2] T. Gazivoda, M. Šokcević, M. Kralj, L. Šuman, K. Pavelić, E. De Clercq, G. Andrei, R. Snoeck, J. Balzarini, M. Mintas, S. Raić-Malić, J. Med. Chem. 50 (2007) 4105-4112.
- [3] S. Raić-Malić, D. Svedruzic, T. Gazivoda, A. Marunović, A. Hergold-Brundić, A. Nagl, J. Balzarini, E. De Clercq, M. Mintas, J. Med. Chem. 43 (2000) 4806-4811.

Acknowledgement:

Financial support from the Croatian Science Foundation under the project No. 5596.